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EXAMINER
LI, QIAN JANICE

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/688,747	BLAU ET AL.	
	Examiner	Art Unit	
	Q. JANICE LI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/12/08*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,8-13,19-21,34 and 39-45* is/are pending in the application.

4a) Of the above claim(s) *46-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3,8-13,19-21,34 and 39-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 September 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/20/09 has been entered.

The amendment, and remarks filed 3/19/09 are acknowledged. Claims 2, 3, 34 have been amended. Claims 2, 3, 8-13, 19-21, 34, 39, 41-50 are pending.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims and new grounds of rejections will not be reiterated. The arguments in 3/19/09 response would be addressed to the extent that they apply to current rejection.

Election/Restrictions

Applicant's previous election with traverse of species drawn to G-CSF as the mobilizing agent, NGF as the neuronal factor, for treating neurodegenerative disorders, and later specifically for producing a purkinje/bone marrow-derived heterokaryon is acknowledged.

In view of claim amendment, claims 2 and 3 have now been rejoined for examination in this application. Claims 46-50 remain withdrawn from consideration.

Claims 2, 3, 8-13, 19-21, 34, 39, 41-45 are under current examination.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. § 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 09/993,045, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Specifically, the parent application is completely silent on **Purkinje neurons and the Purkinje/bone marrow-derived heterokaryon**. Accordingly, the priority date for instantly claimed subject matter, i.e. producing a Purkinje/bone-marrow derived heterokaryon, has been established as the filing date of instant application, i.e. 10/16/2003.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 3, 8-13, 19-21, 34, 39, 41-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are vague and indefinite because of the claim (34) recitation "*a Purkinje/bone marrow-derived heterokaryon*". It appears *a cell* of bone marrow but not the entire bone marrow could derive a Purkinje cell heterokaryon.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 3, 8-13, 19-21, 34, 39, 41-45 stand and newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for reasons of record and following.

Claim 34 is directed to a method of administering agent to "an individual having a deficiency of Purkinje neurons", and claim 2 listed various disorders that caused the Purkinje neuron deficiency. The specification states:

> The invention relates generally to the treatment of neurological disorders, and more particularly to the treatment of neurological conditions characterized by a loss of neurons, damaged neurons, or neurons with inadequate or suboptimal function in the peripheral and/or central nervous system.

The specification then states:

> Purkinje cells play vital roles in maintaining balance and regulating movement. A loss of Purkinje cells results in deficits in these functions in several disorders: ataxia-telangiectasia, the most common cause of progressive ataxia in infancy; Menkes' Kinky Hair syndrome; the alcoholic cerebellar degenerations, particularly Wernicke-Korsakoff syndrome; and various prion diseases including scrapie, Creutzfeldt-Jakob, and Kuru.

Given the broadest reasonable interpretation in light of the specification, instant claims are directed to treating neurological disorders, particularly those as listed above via supplying new Purkinje neurons. However, the specification is completely silent with regard to the effects of the bone marrow mobilization therapy on the recited disorders, and whether any heterokaryon formation could be shown following administration of G-CSF and NGF. As such, the specification fails to provide an enabling disclosure for the intended use.

Concerning the enablement of Purkinje heterokaryon formation following the G-CSF mobilization therapy, the applicant asserts in the Remarks filed March 2009 that example 4 of the specification as filed makes it clear that increasing the number of *mobilized* bone marrow cells causes an increase in heterokaryon formation. To this end, the Office noted on record that example 4 of the specification deals with stem cell transplantation via tail vein injection, not via a

stem cell mobilization agent. However, considering both measures (BMT and BM mobilization) increase circulating stem cells, this ground of rejection is currently withdrawn in favor of the rejections under 35 USC 102 and 103. However, the lack of enablement rejection still stands on the ground of treating neurological disorders by supplying new Purkinje neurons.

Assuming *arguendo*, a few heterokaryon had been formed following the administration of G-CSF as in the case of stem cell transplantation, the specification fails to teach whether the new Purkinje neurons could bring about any clinical beneficial effects on any of the neurological disorders and it fails to establish any of the aforementioned disease could be alleviated by the claimed invention.

First, considering art-known disorders primarily associated with Purkinje neurons such as those listed in the specification, it was known in the art ataxia-telangiectasia is an inherited disease which affects many parts of the body, wherein the gene altered in A-T played a role in DNA damage recognition, the pathology of the disease is attributed to chromosomal instability, abnormalities in genetic recombination, and defective signaling to programmed cell death and several cell cycle checkpoints activated by DNA damage". Hence, it is highly unlikely that supplying a few new Purkinje neurons would translate into any clinical benefit, since the new neurons may quickly become the victim of defective programmed cell death. As to the Prion diseases including scrapie, CJD and Kuru, the current state of the art is such that "ALL ARE CURRENTLY

UNTREATABLE AND ARE **ALWAYS FATAL**" (Wikipedia 2008). In fact, *Na et al*. (Neurosci Let 2009; 449:66-70) teaches scrapie-infection induces neuron progenitor cells spontaneously undergoing neuron regeneration in mice brains. However, the neuron regeneration has not change the untreatable fate of the disease. *Vilette* (Vet Res 2008;Jul-Aug;39) teaches neuron progenitor cells are prone to scrapie multiplication (e.g. abstract and table I). As such it is highly unlikely the bone marrow mobilization therapy could bring any clinical beneficial effect for treating Prion diseases. To this end, the specification fails to shed new light on the hurdles known in the art, and fails to provide an enabling disclosure for what is now claimed.

Claim 2 is directed to treating an individual having deficiency in Purkinje neurons, wherein said deficiency arises from a list of disorders that are not known in the art to be primarily affecting Purkinje neurons. Hence, such Purkinje neuron deficiency is secondary to the primary diseases at a late stage of the primary disease involving extensive damage to the brain. The treatment to majority of the diseases listed is still limited to symptomatic control and support of life. Hence, without cure of the primary disease, it is unlikely a few new Purkinje neurons could bring about any clinical relieve of the primary disease or secondary symptoms. Although the pathological changes of these disorders include the loss of Purkinje neurons, it was not known and the specification fails to teach that supplementing a few Purkinje cells could bring about a beneficial effect on the recited disorders. Hence, the specification fails to provide an

enabling disclosure showing that the bone marrow mobilization therapy could bring about any detectable beneficial effect on these diseases, and fails to provide an enabling disclosure for the intended use.

Given the broadest reasonable interpretation, claims are directed to generating Purkinje/BM cell heterokaryon in *human* brain via stem cell mobilization therapy. To this end, the specification only provides evidence of Purkinje heterokaryon formation in mice. Neither the specification nor post-filing art of record have establish that such heterokaryon exist in humans. For example, *Crain et al*. (J Neurol Sci 2005;233:121-3) examined female human recipients of bone marrow transplantation from male donors, and found Y-labeled male cells were about 10 fold lower than that of rodent studies. In a further experimental study on buccal cells, the author concluded that the Y-labeled cells could not be explained by fusion or microchimerism (see e.g. the abstract). In a publication by the applicant's group, the authors (*Weimann et al*. PNAS 2003;100:2088-93) could only provide circumstantial analysis that new Purkinje neurons in human brains may have been generated from cell fusion, but they can not rule out the possibility the Purkinje may be generated *de novo*. Accordingly, the specification fails to provide an enabling disclosure to support the full scope of the claims.

Claims 19-21 are directed to administering a bone marrow mobilization agent through local or CNS administration of G-CSF. However, since the target tissue of G-CSF is bone marrow for stem cell mobilization, it was unknown and

the specification fails to establish that direct brain tissue administration or CNS administration is sufficient for mobilizing bone marrow stem cells. Moreover, it was known in the art that systemic administration of G-CSF to patients with traumatic brain injury risks increasing acute inflammation in injured brain (*Whalen*, Crit Care Med 1999;27:1014-8), increasing the chance of cerebral contusion, and contribute to the pathogenesis of traumatic brain injury. This mechanism would also apply to infectious diseases of the brain, wherein acute inflammation is part of the pathogenesis. This is why *Whalen* concluded "WE STRONGLY BELIEVE THAT THE USE OF G-CSF IN HUMANS WITH TBI IS PREMATURE UNTIL ANIMAL STUDIES HAVE DEMONSTRATED, IN MORE THAN ONE SPECIES, WHETHER OR NOT THIS AGENT EXACERBATES ANY ASPECT OF BRAIN INJURY AFTER TRAUMA OR STOKE" (last paragraph). To this end, the specification fails to shed any new light on the issue. Accordingly, the specification fails to establish CNS administration would bring any beneficial but not detrimental effect on the brain of patients suffering from Purkinje neuron deficiency. Accordingly, the specification fails to provide an enabling disclosure to support what is now claimed.

The claims also contemplate combined use of neural factors with G-CSF and other bone marrow mobilization agent. To this end, the state of the art is such that *in vitro* or animal model study showing promising therapeutic effect of neuronal factors often cannot be translated to clinical benefit. *Garcia* (Neurotox Res 2000;2:115-37) teaches,

> Neurotrophic factors are compounds that enhance neuronal survival and differentiation. Most of these compounds exert their pharmacological actions on

> selective types of neurons, and therefore, are considered promising new therapeutic agents for the treatment of different neurodegenerative disorders characterized by selective degeneration of certain neuronal groups. Those compounds have been used in humans for several neurological disorders including amyotrophic lateral sclerosis--ciliary derived neurotrophic factor (CNTF) and brain derived neurotrophic factor (BDNF), Alzheimer's disease and peripheral neuropathy--nerve growth factor (NGF) and Parkinson's disease (PD)--glial derived neurotrophic factor (GDNF). In spite of well founded clinical experiments by previous experimental work in animal models some of these trials have been negative. For instance, animal models of PD have shown that several neurotrophic factors, including GDNF and other compounds, reduce apoptosis and increase resistance of dopamine neurons to neurotoxins in vitro. These compounds prevent or recover the damage to dopamine neurons of rodents and primates produced by chemical or mechanical acute lesions including 6-OH-DA, MPTP, methamphetamine and axotomy. The differences between the promising results obtained in experimental models and the lack of clinical results or excessive toxicity found in humans could be attributed to the following reasons: (a) Lack of relevance between the pathogenesis of the experimental lesion and the corresponding neurodegenerative disorder. (b) Poor correlation between results obtained in acute, self-limited, selective deficit produced to experimental animals and those available in more complex, chronic and progressive disorders involving patients. (c) Inadequate delivery of the active product to the target area in the human brain. (d) Poor information from acute experiments in animals which does not predict long-term effects of chronic infusion in humans. Further experimental work, therefore, is needed to transfer these neurotrophic factors to the clinic. (Emphasis added)

Larkfors (J Neurochem 1996;66:1362-73) teaches, that Purkinje neuron fails to respond to the treatment of NGF (e.g. the abstract).

The specification fails to provide evidence contrary to the observation of *Larkfors* and *Garcia*, and the specification is completely silent with regard to addressing or overcoming the art known hurdles, and hence, the prophetic teaching of the specification fails to provide an enabling disclosure for what is now claimed.

Therefore, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

Response to Arguments

In the remarks, the applicant first argues that there is no explicitly recited limitation of treating disorders in the claims, and alleges that it is improper for the examiner to make enablement rejection based on the non-existing claim limitation.

The argument has been fully considered but found not persuasive.

MPEP 2111 instructs, "DURING PATENT EXAMINATION, THE PENDING CLAIMS MUST BE "GIVEN THEIR BROADEST REASONABLE INTERPRETATION CONSISTENT WITH THE SPECIFICATION." >THE FEDERAL CIRCUIT'S EN BANC DECISION IN PHILLIPS V. AWH CORP., 415 F.3D 1303, 75 USPQ2D 1321 (FED. CIR. 2005) EXPRESSLY RECOGNIZED THAT THE USPTO EMPLOYS THE "BROADEST REASONABLE INTERPRETATION" STANDARD:

> THE PATENT AND TRADEMARK OFFICE ("PTO") DETERMINES THE SCOPE OF CLAIMS IN PATENT APPLICATIONS NOT SOLELY ON THE BASIS OF THE CLAIM LANGUAGE, BUT UPON GIVING CLAIMS THEIR BROADEST REASONABLE CONSTRUCTION "IN LIGHT OF THE SPECIFICATION AS IT WOULD BE INTERPRETED BY ONE OF ORDINARY SKILL IN THE ART." IN RE AM. ACAD. OF SCI. TECH. CTR., 367 F.3D 1359, 1364[, 70 USPQ2D 1827] (FED. CIR. 2004).".

As such, when the claims recite "*administering an agent that mobilizes bone marrow cells to an individual having a deficiency of Purkinje neurons*", and "*wherein said Purkinje neuron deficiency arises from a disorder* ….", the intended

use is apparent in light of the specification. Moreover, when the claims dedicating an entire page to list various diseases and disorders associated with Purkinje neuron deficiency, and when claim 21 explicitly require administering G-CSF into a human individual, it is disingenuous of the applicant to assert that the limitation of treating a neurological disorder is “non-existing” and is not embraced/intended by the claims. Accordingly, the standard applied to evaluate instant claims is rightfully appropriate.

Further, from the teaching of the skilled as taught by *Garcia*, the state of the art is such in the context of neuronal degenerative disease model and human disease, there was a lack of relevance between the pathogenesis of the experimental lesion and corresponding neurodegenerative disorder; there was poor correlation between results obtained in acute, self-limited, selective deficit produced to experimental animals and those available in more complex, chronic and progressive disorders involving human patients, and there was inadequate delivery of the active product to the target area in the human brain, and there was poor information from acute experiments in animals which does not predict long-term effects of chronic infusion in humans. In view of such state of the art, and the disclosure provided by the applicant, instant claims remain in the realm of speculation.

Therefore, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 2, 3, 34, 39, 41-45 are rejected under 35 U.S.C. 102(b) as being unpatentable over *Ishikawa et al.* (J Trauma, Injury Infect Crit Care 1999;46:999-1008).

Ishikawa teaches a method of treating head trauma comprising administering G-CSF to the patient, wherein the G-CSF would mobilizes bone marrow cells and subsequently producing a Purkinje/bone marrow-derived heterokaryon. Accordingly, *Ishikawa* anticipate instant claims.

It is noted in this and following rejection, the art does not teach G-CSF mobilization, generating bone marrow cell-derived Purkinje neuron or through the mechanism of cell fusion and formation of a heterokaryon. However, the recited limitation is a description of the intended use and mechanism for generating bone marrow cell-derived Purkinje neuron, which does not result in a manipulative difference in terms of the positive method steps when compared to the prior art method. If the prior art method is capable of performing the intended use, i.e. producing a Purkinje/bone marrow-derived heterokaryon via G-CSF administration, then it meets the claim. **In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).**

Claims 2, 3, 34, 39, 41-45 are rejected under 35 U.S.C. 102(b) as being unpatentable over *Rudolf et al.* (J Neural Transm 1997;104:1305-11).

Rudolf teaches a method of treating patients with Parkinson's disease and dopaminergic psychosis comprising administering G-CSF to the patient, wherein the G-CSF would mobilizes bone marrow cells and subsequently producing a Purkinje/bone marrow-derived heterokaryon. Accordingly, *Rudolf* anticipate instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 3, 34, 39, 41-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Priller et al*. (J Cell Biol 2001;155:733-8), in view of *Molineux et al.* (Blood 1990;76:2153-8).

Priller reports producing cerebellar Purkinje neurons in mouse brains 12-15 months after bone marrow transplantation, wherein the Purkinje neurons were derived from GFP gene-marked bone marrow cells, express Purkinje-specific gene D28K but not glial markers Ibl and functional (e.g. the abstract, column 2 of

page 734 to p735 and figure 4). *Priller* goes on to teach the significance of the finding and potential clinical applications for CNS disorders that are associated with Purkinje cell loss (col 2, page 736), which may embrace all of the disorders listed in claim 2. *Priller* also points to a previous study wherein bone marrow transplantation in a mouse model of Niemann-Pick disease led to reduced ataxia and increased life span.

Priller does not teach using an agent that mobilizes bone marrow cells in place of bone marrow transplantation.

Molineux supplemented *Priller* by establishing it was well known in the art long before instant filing date that the blood of G-CSF treated patients provides a convenient source for autologous transplantation of the most primitive stem cells (e.g. the abstract and conclusion). *Molineux* reported that G-CSF treated blood is at least comparable if not superior to normal blood in terms of the numbers of the stem cells and the ability of generating differentiated cells in blood, bone marrow and spleen (e.g. tables 3-5). *Molineux* concluded "THE DISTRIBUTION OF THE DONOR CELLS IN THE TRANSPLANTED RECIPIENT AND THEIR ABILITY TO SUSTAIN THE PRODUCTION OF CFU-S, SUGGEST THAT THE MOST PRIMITIVE RECONSTITUTING STEM CELLS ARE RELEASED INTO THE BLOOD FOLLOWING TREATMENT WITH G-CSF" and "A GRAFT OF CELLS FROM PERIPHERAL BLOOD OF RHUG-CSF TREATED MICE APPEARS, THEREFORE, TO BE AS EFFECTIVE AS A GRAFT FROM NORMAL BONE MARROW CELLS…" (see the last two paragraphs of the article).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by *Priller* by

adopting G-CSF mobilization in place of bone marrow transplantation as taught by *Monlineux* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the mobilization method would obviate the need for a surgical procedure and an appropriate donor. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 8-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Priller et al*. (J Cell Biol 2001;155:733-8), in view of *Molineux et al.* (Blood 1990; 76:2153-8) as applied to claims 2, 3, 34, 39, 41-45 above, further in view of *Martinez-Murillo et al*. (Neurosci 1993;52:587-93).

The combined teaching of *Priller* in view of *Molineux* does not teach combining the G-CSF mobilization with a neuronal factor.

Martinez-Murillo supplemented the deficiency by establishing it was well known in the art that NGF plays a role on Purkinje cell recovery after damage. *Martinez-Murilloet* teaches Purkinje cells respond to injury by increasing surface expression of the low-affinity nerve growth factor receptor, suggesting that increased level of NGF may be beneficial for purkinje cell recovery in adulthood (e.g. Figures and discussion).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by *Priller* in view of *Molineux* by including a nerve growth factor as taught by *Martinez-Murillo* with

a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the benefit for neuron protection. As to the means and timing of administering of the two agents, they fall within the bounds of optimization. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. JANICE LI** whose telephone number is **571-272-0730**. The examiner can normally be reached on 9 AM -7:00pm, Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

/Q. JANICE LI, M.D./
Primary Examiner, Art Unit 1633

QJL
July 10, 2009